BMJ Open Effect of repetitive transcranial magnetic stimulation on patients with severe depression: a study protocol for systematic review and meta-analysis of randomised clinical trials

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To cite: Han F, Tao S, Liang S, *et al.* Effect of repetitive transcranial magnetic stimulation on patients with severe depression: a study protocol for systematic review and meta-analysis of randomised clinical trials. *BMJ Open* 2021;11:e050098. doi:10.1136/bmjopen-2021-050098

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-050098>).

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Received 09 February 2021
Accepted 17 November 2021

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ABSTRACT

Introduction Depression is characterised by easy recurrence, high disability and high burden, and antidepressant therapy is the standard treatment. However, its treatment effect on patients with severe depressive disorder has been unsatisfactory. Previous studies have shown that repetitive transcranial magnetic stimulation (rTMS), as a neurotherapy, can effectively mitigate the severity of depressive symptoms. Yet, more evidence is still required for TMS to treat severe depression. This study will be the first systematic review of the efficacy and tolerability of TMS for treating severe depression. We expect it to guide future clinical practice of TMS for the treatment of psychiatric disorders.

Methods and analysis We will search for the randomised controlled trial (RCT) involving rTMS for treating depression in eight electronic databases, including PubMed, Web of Science, EMBASE, the Cochrane Library and Wanfang Database, from publication up to September 2021. We will define Improvement in depressive symptoms, the difference between pretreatment (baseline) and post-treatment as the primary outcomes. The difference between pretreatment and post-treatment changes in resting state fMRI will be regarded as the secondary outcomes. Quality assessment of the included articles will be independently performed according to the Cochrane Risk of Bias tool.

Ethics and dissemination Ethical approval is not essential because there is no need to collect individual patient data. And this study will be published in a peer-reviewed journal.

Trial registration number CRD42020211460.

INTRODUCTION

Depression, featuring easy relapse, high disability rate and heavy burden, is a common mental system disease with a long course. Depression affects more than 300 million people in the world. Based on the WHO, depression is an immense burden of non-fatal health consequences, accounting for approximately 12% of the total life of disability.^{1–3}

Strengths and limitations of this study

- This study will provide the first systematic review and meta-analysis for evaluating the efficacy of repetitive transcranial magnetic stimulation (rTMS) for severe depression.
- Since most randomised controlled trials (RCTs) on rTMS for severe depression have a small sample size, the present study will provide more reliable evidence for clinical management.
- The electronic search will only include RCTs published in Chinese and English that could limit the inclusion of studies.

It usually requires long-term maintenance therapy to prevent future emotional episodes as the primary goal of treatment. Antidepressant therapy is a standard method for the treatment of depression.⁴ However, it does not work for everyone with depression. Depression in these patients is usually termed as severe depressive disorder (SDD), which is defined as after two or more antidepressant treatments, the 17-item Hamilton Depression Rating Scale (HAM-D-17) score reduction rate was less than 20%.^{5 6}

The traditional treatment for SDD is facing challenges. Patients' quality of life can be significantly compromised, including sleep and work. Although pharmacotherapy and psychotherapy are effective for depression nowadays, only 33% of patients achieve a complete remission with medication during treatment in the acute phase, with less than 50% of patients failing to achieve remission after multiple medication trials.^{7 8} Besides, these treatments often do not work with the depressive symptoms. However, approximately 30% of patients with depression receive extensive psychotherapy (although

around 20% in 2006 received psychotherapy). Previous resistance to antidepressants also reduces the likelihood of responding to subsequent interventions. Thus, many patients require better alternative treatment options for depression.

Repetitive transcranial magnetic stimulation (rTMS) was first demonstrated to treat depression in the mid-1990s as a neurotherapy. rTMS uses the principle of induction to transmit electric current to the brain through the resistance layer of the scalp, skull and meninges, where it can change the electrical environment of neurons and cause neurons to discharge.^{9 10} rTMS is applied to the prefrontal cortex and induces magnetic fields, leading to depolarisation of potential neurons and regulation of neural circuits involved in emotion regulation and depressive symptoms.^{11–13} Due to its advantages, including being non-invasive, safe, with minimal discomfort and convenient operation, rTMS has captured the attention of scientists, clinicians, and lay observers since its commercial advent in 1985.¹⁰ In addition, a metasystematic review including 18 studies has shown that accelerated TMS is effective in improving depressive symptom severity.¹⁴

However, doubts about rTMS's effectiveness in treating severe depression still need to be cleared with more evidence. Since the relevant evidence is rare, in our study, we will perform the first systematic review and meta-analysis to investigate the efficacy and tolerance of rTMS in the treatment of severe depression. Based on our summary of the literature, we expect it can guide the clinical practice of rTMS on the treatment of mental system disease in the future.

METHODS

Patient and public involvement

Patients or the public were not involved in the design, conduction, reporting or dissemination plans of our research.

Study registration

The protocol of this review will be conducted and reported referring to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement guidelines (see online supplemental appendix 1). The protocol has been registered on the PROSPERO.

Study selection

Type of studies

We will evaluate the articles based on criteria of the review target and participants, interventions, comparisons and outcomes. Only randomised and controlled trials involving participants with TMS versus other treatments, placebo or sham treatment were included in this review. The language of the literature will be limited to Chinese and English. Studies that mentioned the term 'randomisation' will be considered. Other designs such as case reports and non-randomised controlled trials will

be excluded. Studies that used incorrect randomisation methods (eg, pseudorandomisation) will be excluded.

Type of participants

Inclusion criteria

(1) Subjects referring to the diagnostic and Statistical Manual of mental disorders (4th edition), the diagnostic criteria of the depressive episode were met; (2) subjects were assessed with Hamilton Depression Scale Item 3, and score ≥ 2 points¹⁵; (3) subjects were assessed with Suicidal Ideation Scale, and score > 12 points, but refused to accept point convulsion treatment¹⁶; (4) subjects signed informed consent.

Exclusion criteria

(1) Participants with a history of severe physical disease, organic brain disease, depression caused by other psychoactive substances and independent substances (eg, alcohol or drugs); (2) participants with brain surgery and epilepsy history; (3) participants who adjust drug dosage during treatment; (4) participants with metal or electronic devices built into the body; (5) participants who have been treated with modified electroconvulsive therapy in the past 3 months; (6) participants in pregnancy or breastfeeding period, and those who refused to sign the informed consent.

Type of interventions

We will consider studies evaluating the treatment of rTMS (with different frequencies in Hz, stimulation intensity, total stimuli, pulses per session, sessions per day, inter-session interval in minutes, trains per session, the intertrain interval in seconds).

Type of comparators

We will include and categorise the comparators in the study as follows: (1) rTMS versus sham rTMS, (2) rTMS versus placebo, (3) rTMS versus waiting list/usual care/no treatment. Articles comparing different rTMS will be removed.

Outcome measures

Primary outcomes

We will define improvement in depressive symptoms (eg, decline on the HAMD or Suicidal Ideation Scale Score), that is, the difference between pretreatment (baseline) and post-treatment, as the primary outcomes.

Secondary outcomes

Except for the changes in resting state fMRI, other differences before and after treatment will be considered as secondary results.

Search strategies

An electronic search will be carried out in the following databases: PubMed, Web of Science, EMBASE, the Cochrane Library and WAN FANG from publication up to September 2021. We will use the terms of medical subjects (MeSH) and keywords individually or in combination on

PubMed (see online supplemental appendix 2) during the query. However, the search strategy for other databases will be slightly modified.

Study selection

Two reviewers will assess the titles and abstracts of all studies separately for use by potential candidates. Reduplicated studies will be deleted. After screening the titles and abstracts, full-text copies of all eligible studies will be downloaded for reassessment. In the event that a reviewer is uncertain about the eligibility of any study, the full text will be acquired for re-examination. In case of disagreement, a third reviewer will be consulted. Excluded studies and reasons for exclusion will be recorded. The specific research screening process will be shown in the PRISMA flow diagram.

Data extraction

Two investigators will perform data extraction independently. Characteristics of studies, participants, methods, interventions, results, outcomes, adverse events, conflicts of interest, ethical recognition and other necessary information will be extracted. If the reported data are insufficient, the corresponding authors or relevant authors will be contacted by email. Besides, any disagreement will be settled by discussion between the two authors, and a third author will be invited for further judgement of the disputes.

Risk of bias assessment

The authors will assess the risk of bias using RoB V.2.0 of Cochrane Collaboration Evaluation of all included studies.¹⁷ The following areas of bias risk will be assessed: sequence generation, hidden distribution of sequences, blinding of participants, personnel and outcome evaluators, incomplete result data, selective results reporting and other sources of bias. The judgement of these projects will be divided into three levels: 'low risk of bias', 'high risk of bias' and 'unclear risk of bias'. Conflicts of any differences will be discussed, or another reviewer will review these conflicts to facilitate a consensus.

Quality of evidence assessment

According to the recommended evaluation, development and evaluation classification method, evaluating the quality of evidence for important outcomes can be divided into four levels: high quality, medium quality, low quality and very low quality.^{18 19} The basis of risk of bias, inconsistency, indirectness, inaccuracy and publication bias is the way how evidence quality is generally judged.

Measures of effects

We will use the Review Manager software V.5.3 to carry out the statistical analysis. Mean difference (MD) or standardised MD will be used for continuous data. Risk ratio (RR) or risk difference will be used to analyse dichotomous data. Each parameter's corresponding 95% CI will be calculated between the treatment and control groups.

Assessment of heterogeneity

We leveraged Cochrane's Q test to examine whether significant interstudy heterogeneity exists. It is assessed via the computed I^2 statistic, where values >50% indicated moderate heterogeneity. We employed a random effects model to calculate summary MD and RR and 95% CI regardless of heterogeneity.

Assessment of reporting bias

The reporting bias will be evaluated using a funnel plot when more than 10 tests are included.

Sensitivity analysis

Monitoring the robustness of the primary decision made in the review process can be the sensitivity analysis results. Multiple decision points will be taken, such as sample size, methodological weakness and missing data. Finally, we will discuss the risk of bias in the review process indicated by the sensitivity analysis results.

Subgroup analysis

When data are available and considerable heterogeneity is detected, a subgroup analysis will be carried out consulting variations in the characteristics of the trial participants, rTMS treatment, the amplitude of low-frequency fluctuation and functional connectivity density.

Ethics and dissemination

No ethical approval is required because the publications included in our study do not involve patients' privacy. The primary data will be from the published literature. This study does not involve human participants.

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Funding This work was supported by Post-doctoral Scientific Research Fund (303044) and National Key R&D Program of China (2018YFC2001700).

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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